Date: 30 March 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Nubeqa

International non-proprietary name: darolutamid

Pharmaceutical form: film-coated tablet

Dosage strength(s): 300 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Bayer (Schweiz) AG

Marketing Authorisation No.: 67521

Decision and Decision date: extension of therapeutic indication approved on 17 January 2023

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARI	Androgen receptor inhibitor
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CT	Computed tomography
CRPC	Castration-resistant prostate cancer
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
G3-4	Grade 3-4
G5	Grade 5
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
LHRH	Luteinising hormone-releasing hormone
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
mPC	Metastatic prostate cancer
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable

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NCCN	National Comprehensive Cancer Network
NHA	New hormonal agents
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PC	Prostate cancer
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event-free survival
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
WBC	White blood count

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and Dosage

2.2.1 Requested Indication

Treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

2.2.2 Approved Indication

NUBEQA, in combination with docetaxel and androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC), for whom docetaxel therapy is indicated (see "Clinical efficacy").

2.2.3 Requested Dosage

Summary of the applied standard dosage:
NUBEQA 600 mg, (two 300 mg tablets) administered orally twice daily. Swallow tablets whole. Take NUBEQA with food.

mHSPC patients should receive NUBEQA in combination with docetaxel. The first of six cycles of docetaxel should be administered within six weeks of the start of NUBEQA treatment.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	21 March 2022
Formal control completed	1 April 2022
Preliminary decision	22 September 2022
Response to preliminary decision	21 October 2022
Labelling corrections	30 November 2022
Response to Labelling corrections	20 December 2022
Final Decision	17 January 2023
Decision	approval

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3 Medical Context

Prostate cancer (PC) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020, accounting for 14% of all cancers diagnosed. For patients diagnosed with metastatic disease, the overall 5-year survival rate is about 30 to 35%.
Androgen deprivation therapy (ADT) is the gold standard for the treatment of metastatic PC (mPC). The goal is to lower testosterone to a castrate level, given the critical role circulating androgens play in the progression of metastatic prostate cancer. Primary ADT can be accomplished using bilateral orchiectomy (surgical castration), or medical castration with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist, or an LHRH agonist plus a first-generation anti-androgen / androgen receptor inhibitor (ARI).
First-line treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) and high-volume or high-risk disease consists of ADT plus docetaxel, if the patient is a candidate for docetaxel. For most patients with hormone-sensitive, low-risk/low-volume metastatic prostate cancer, ADT plus new hormonal agents (NHA) or ADT plus two systemic agents are recommended rather than ADT alone. In patients with high-risk/high-volume disease who are not candidates for docetaxel (e. g. due to comorbidities), this approach is also an option.

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4 Nonclinical Aspects

The applicant did not submit new nonclinical studies with the initial submission to support the requested extension of the indication. In response to Swissmedic's stipulations, the applicant provided a dose range-finding and a pivotal study to determine the toxicity and carcinogenicity potential of darolutamide in CByB6F1-Tg(HRAS)2 Jic mice. No carcinogenic potential was observed for animals administered up to 500 mg/kg/dose twice daily. The studies provided were considered acceptable since there are no changes with regard to posology and method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and corresponding product information from the FDA were used as a basis for the clinical pharmacology evaluation.
The PK of darolutamide in combination with docetaxel has been characterised as part of the ARASENS study. No clinically meaningful change in darolutamide exposure in the mHSPC population, relative to the non-metastatic castration-resistant prostate cancer population, and no clinically relevant drug-drug interaction between darolutamide and docetaxel has been observed.
For further details concerning clinical pharmacology, refer to the information for healthcare professionals.

5.2 Dose Finding and Dose Recommendation

No specific dose-finding study was performed for the combination of darolutamide plus docetaxel. The twice daily dose regimen of darolutamide 600 mg (of note: evaluated as monotherapy) was selected based on previous findings from dose escalation and dose-finding study 17829 (ARADES), which investigated doses of darolutamide ranging from 100 to 900 mg twice daily in metastatic castration-resistant prostate cancer (mCRPC). Dose levels lower than 600 mg twice daily were not studied in mHSPC patients.

5.3 Efficacy

The applicant provided efficacy results from one pivotal study (ARASENS). The ARASENS study was an international, randomised, double-blind, placebo-controlled Phase 3 study of darolutamide versus placebo in addition to standard ADT and docetaxel in patients with mHSPC.
Patients with adenocarcinoma of the prostate and metastatic disease confirmed by central radiology review were eligible. Patients needed to be candidates for ADT and docetaxel therapy, per the investigator's judgment. Patients were randomised 1:1 to either darolutamide plus ADT and docetaxel or placebo plus ADT and docetaxel in a double-blinded fashion. The contribution of docetaxel to the treatment effect of darolutamide and ADT cannot be assessed because no third treatment arm with darolutamide and ADT (without docetaxel) was assessed. Patients who had undergone prior treatment with LHRH agonist/antagonists (started > 12 weeks before randomisation), second generation AR inhibitors (such as enzalutamide), CYP17 enzyme inhibitors (such as abiraterone), chemotherapy or immunotherapy for prostate cancer were excluded.
Stratification factors were extent of disease (M1a – non-regional lymph node metastases only vs. M1b – bone metastases with or without lymph node metastases vs. M1c – visceral metastases with or without lymph node metastases or with or without bone metastases) and alkaline phosphatase level (ALP) (< ULN vs.≥ ULN). Darolutamide 600 mg (2 tablets of 300 mg) twice daily (BID) was administered, equivalent to a total daily dose of 1200 mg (or matching placebo). Docetaxel was administered at a dose of 75 mg/m^2 as an intravenous (IV) infusion every 21 days for 6 cycles, starting within six weeks of starting the study drug. Treatment was to be continued until progression, unacceptable toxicity or death. Docetaxel is authorised in Switzerland for castration-resistant prostate cancer only. However, treatment with docetaxel in combination with ADT is recommended by international guidelines (NCCN, EAU, ESMO) for patients with mHSPC and high-volume/high-risk disease. Based on the positive Phase 3 studies CHAARTED and STAMPEDE, this combination is also recommended by the Swiss "Interdisziplinäre Schweizerische Konsensempfehlungen" [multidisciplinary Swiss consensus recommendations]. Therefore, the comparator arm is considered acceptable.
Screening assessments included both contrast-enhanced chest, abdomen and pelvic CT or MRI and bone scan, which could be within 42 days prior to the start of study treatment. There was no scheduled regular radiological assessment of tumour response.

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The primary endpoint of the ARASENS study was overall survival (OS), defined as time from the date of randomisation until death from any cause. Secondary endpoints included in the hierarchical testing procedure were time to castration-resistant prostate cancer (CRPC), time to pain progression, symptomatic skeletal event-free survival (SSE-FS), time to first symptomatic skeletal event (SSE), time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms and time to initiation of opioid use for ≥7 consecutive days.

Results were presented after a median follow-up time of 43.7 months in the darolutamide arm and 42.4 months in the placebo arm.
Overall n=1686 patients were enrolled and n=1306 were randomised, with 651 patients in the darolutamide arm and 654 patients in the placebo arm in the full analysis set (FAS). At data cut-off, 45.9% of patients in the darolutamide arm vs. 19.1% of patients in the placebo arm were ongoing with study treatment.

Demographics and baseline characteristics were generally well balanced between the treatment arms. The median age was 67 years in both arms, patients were mostly White (darolutamide 53.0%; placebo 50.9%), or Asian (darolutamide 35.3%, placebo 37.5%), and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (darolutamide 71.6%, placebo 70.6%).
All patients had metastatic stage disease at study entry, most of them had stage M1b (darolutamide 82.9% vs. placebo 82.7%). The rate of patients with M1c was 13.8% in the darolutamide arm and 13.9% in the placebo arm; the rate of patients with M1a was 3.5% in the darolutamide arm and 3.4% in the placebo arm. The majority of patients presented with de novo metastatic disease (darolutamide 85.7%; placebo 86.5%). Prior systemic antineoplastic therapy included ADT and first-generation ARIs such as bicalutamide.

The primary endpoint of overall survival (OS) was statistically significant in the darolutamide arm compared to placebo (hazard ratio (HR): 0.68; 95% CI: [0.57; 0.80], one-sided p<0.0001). Median OS was not reached in the darolutamide arm (95% CI: [A; A]) and was 48.9 months in the placebo arm (95% CI: [44.4; A]). The number of OS events was 35.2% in the darolutamide arm and 46.5% in the placebo arm.

See information for healthcare professionals for further information on efficacy.

5.4 Safety

The analysis of safety is based on the results of the ARASENS pivotal study.
The number of patients with any treatment-emergent adverse events (TEAE) was similar in both treatment arms (darolutamide 99.5%, placebo 98.9%). The most frequent events (≥ 20%) in the darolutamide arm were alopecia (40.5%), fatigue (33.1%), anaemia (27.8%), arthralgia (27.3%), peripheral oedema (26.5%), decreased neutrophil count (26.1%), diarrhoea (25.6%), decreased white blood count (WBC) (23.8%) and constipation (22.5%).
Grade 3-4 (G3-4) TEAEs were reported in a slightly higher proportion of patients in the darolutamide arm compared to placebo (66.1% vs. 63.5%).
The most common G3-4 TEAEs (≥5% of patients in either treatment arm) in the darolutamide and placebo arms were decrease neutrophil count (23.2% vs. 21.5%), decreased WBC count (16.9% vs. 14.9%), neutropenia (8.6% vs. 10.5%), febrile neutropenia (7.8% vs. 7.4%), hypertension (6.4% vs. 3.2%) and anaemia (4.8% vs. 5.1%).

More patients in the placebo arm (n=304, 46.8%) died compared to the darolutamide arm (n=229, 35.1%), mostly due to progressive disease (234/304 and 170/229).
Grade 5 (G5) TEAEs were reported at a similar rate in both treatment arms (n=27 [4.1%] patients in the darolutamide arm and n=26 [4.0%] in the placebo arm). The most frequent reasons in the darolutamide arm were COVID-19 pneumonia or COVID-19 (n=5) and sudden death (n=2).

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Serious adverse events (SAEs) were reported at a slightly higher rate of 44.8% in the darolutamide arm compared to 42.3% in the placebo arm. The most frequently reported SAEs in both arms were haematological and infectious toxicities.

TEAEs leading to discontinuation of the study drug were reported in 13.5% of patients in the darolutamide arm and in 10.6% of patients in the placebo arm.

Secondary primary malignancies were reported at a slightly higher rate in the darolutamide arm compared with placebo (3.8% vs. 2.5%).

QTcF values beyond 500 ms at the end of treatment were observed more frequently in the darolutamide arm compared to the placebo arm (3.2% vs. 1.1%).

One case of potential drug-induced liver injury (DILI) was identified in the darolutamide arm of the ARASENS study. After a review of cumulative data from clinical studies and post-marketing sources, there was reasonable suspicion of a causal association between darolutamide and increased ALT/AST indicative of hepatocellular liver injury as reported by the applicant. A specific warning was added to the “Warning and precautions” section of the information for healthcare professionals.

5.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Darolutamide (Nubeqa®) is an orally administered non-steroidal androgen receptor inhibitor (ARI) that has been authorised in Switzerland in combination with androgen deprivation therapy (ADT) in the first-line setting for non-metastatic castration-resistant prostate cancer (nmCRPC) since 2020. Currently, upfront combination therapies with ADT are the standard of care in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Docetaxel in combination with ADT for mHSPC is recommended by international guidelines (NCCN, EAU, ESMO) for patients with high-volume/high-risk disease.

For the assessment of efficacy and safety, the applicant submitted one pivotal, randomised, double blind, placebo-controlled, Phase 3 study (ARASENS) investigating 1306 patients.

A statistically significant improvement in the primary endpoint of OS was demonstrated in patients randomised to receive darolutamide plus docetaxel and ADT compared with placebo plus docetaxel and ADT.
The study population consisted of patients with high-volume/high-risk disease (defined as presence of visceral metastases and/or ≥4 bone metastases, or Gleason score ≥8 disease, or de novo metastatic disease at presentation); therefore, the indication was specified to reflect the population with a need for docetaxel therapy.
The overall safety profile for darolutamide in the mHSPC population in ARASENS was generally consistent with the safety profile previously observed in the non-metastatic CRPC population in ARAMIS, treated with darolutamide plus ADT.
Based on the data available, the combination of darolutamide plus docetaxel provides clinically meaningful benefit in terms of a relevant overall survival advantage in this target population with advanced-stage disease. The combination has an acceptable and manageable safety profile.
Overall, the benefit-risk assessment is positive.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nubeqa was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document which is valid and relevant for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

NUBEQA®

Composition

Active substances

Darolutamide.

Excipients

Calcium hydrogen phosphate, sodium croscarmellose (produced using genetically modified cotton) equivalent to sodium 2.7 mg, lactose monohydrate 186 mg, magnesium stearate, povidone K 30, hypromellose 15 cP, macrogol 3350, titanium dioxide (E 171) q.s.p. 1 film-coated tablet.

Pharmaceutical form and active substance quantity per unit

White to off-white, oval, film-coated tablets 16 mm long and 8 mm wide, marked with “300” on one side and “BAYER” on the other side.
Each film-coated tablet contains 300 mg darolutamide.

Indications/Uses

NUBEQA, in combination with androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with non-metastatic, castration-resistant prostate cancer (nmCRPC) at high risk of developing metastases (especially with a PSADT ≤ 10 months; see “Clinical efficacy”).

NUBEQA, in combination with docetaxel and androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC), for whom docetaxel therapy is indicated (see “Clinical efficacy”).

Dosage/Administration

Usual dosage

nmCRPC and mHSPC
NUBEQA is for oral use. The recommended dose is 600 mg (two 300 mg film-coated tablets) of darolutamide twice daily, equivalent to a total dose of 1200 mg per day.
The tablets must be taken whole together with a meal (see section “Pharmacokinetics”).
Treatment with NUBEQA must be continued until disease progression or unacceptable toxicity occurs.

Patients receiving NUBEQA should also concurrently receive a luteinising hormone-releasing hormone (LHRH) analogue or should have had bilateral orchiectomy.
If a dose of NUBEQA is missed, it should be taken as soon as the patient remembers prior to the next scheduled dose. The patient must not take two doses together to make up for a missed dose.

mHSPC
Treatment with NUBEQA in patients with mHSPC must be initiated in combination with docetaxel (see section “Clinical efficacy”). The first of 6 docetaxel cycles should be administered within 6 weeks after initiation of NUBEQA treatment. The recommendations in the Information for healthcare professionals for docetaxel should be followed. Treatment with NUBEQA should be continued until disease progression or unacceptable toxicity occurs, even if the administration of any docetaxel cycle is delayed, interrupted or discontinued.

Dose adjustment due to adverse reactions/interactions

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction associated with NUBEQA, administration should be discontinued or the dose reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.
Dose reduction below 300 mg twice daily is not recommended. The maximum effective daily dose is the recommended dose of 600 mg twice daily (see section “Pharmacokinetics”).

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required for patients with mild hepatic impairment.
The available data on the pharmacokinetics of darolutamide in moderate hepatic impairment are limited.
Darolutamide has not been studied in patients with severe hepatic impairment (see also section “Pharmacokinetics”).
In patients with moderate to severe hepatic impairment (Child-Pugh classes B and C), the recommended starting dose is 300 mg twice daily.

Patients with renal disorders

No dose adjustment is required in patients with mild to moderate renal impairment.
In patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily.

Elderly patients

In clinical studies, no clinically relevant differences with regard to safety or efficacy were observed between elderly patients aged 65-74 years, 75-84 years or ≥ 85 years and younger patients

(< 65 years). No dose adjustment is therefore necessary in elderly patients (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of NUBEQA in children and adolescents below 18 years of age have not been established.

Genotype/genetic polymorphisms

No clinically relevant differences were observed across ethnic groups. No dose adjustment is necessary based on ethnicity (see section “Pharmacokinetics”).

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- In women who are pregnant or of childbearing potential.

Warnings and precautions

Hepatic transaminase elevations

In clinical studies with NUBEQA, cases of idiosyncratic hepatic reactions have been reported, with increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to 5 and 20 x upper limit of normal (ULN), respectively. Time to onset of this reaction ranged from 1 month to 10.5 months after initiation of NUBEQA therapy. The ALT and AST elevations were reversible upon discontinuation of NUBEQA. In case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to NUBEQA, NUBEQA must be permanently discontinued (see section “Undesirable effects”).

ADT can prolong the QT interval

In patients with risk factors such as a history of QT prolongation, torsade de pointes, hypokalaemia, or in patients on treatment with medicinal products that prolong the QT interval (see section “Interactions”), ECG monitoring should be performed at the start of treatment and at regular intervals during treatment.

Contraception for men and women

If the patient is sexually active with a woman of childbearing potential, he should use a highly effective method of contraception during treatment with NUBEQA and for up to 1 week after the end of treatment, in order to prevent a pregnancy.
If the patient is sexually active with a pregnant woman, a condom must be used during treatment with NUBEQA and for up to 1 week after the end of treatment. Exposure of the fetus to an androgen

receptor inhibitor through seminal transfer to the pregnant woman has to be avoided, as this could affect development of the fetus.

Changes in bone mineral density

In the clinical studies with darolutamide, there were no studies on bone mineral density. It can be assumed that long-term testosterone suppression during treatment with darolutamide has an impact on bone mineral density. A decrease in bone mineral density has been reported in patients treated with GnRH agonists and in patients post orchiectomy.

Recent cardiovascular disease

Patients with a clinically relevant cardiovascular disease in the previous 6 months, including stroke, myocardial infarction, severe/unstable angina pectoris, coronary or peripheral artery bypass surgery and symptomatic cardiac failure, were excluded from the clinical studies. Hence, the safety of darolutamide in these patients has not been established. When NUBEQA is prescribed, patients with clinically relevant cardiovascular disease should be treated according to the current guidelines for such diseases.

This medicine contains less than 1 mmol sodium (23 mg) per oral dose (2 film-coated tablets), that is to say essentially “sodium-free”.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Interactions

Effect of NUBEQA on other medicinal products

Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 substrates
Darolutamide is an inhibitor of BCRP, as well as OATP 1B1 and 1B3.
Administration of darolutamide (600 mg twice daily for 5 days) prior to concomitant ingestion of a single dose of rosuvastatin (5 mg), together with food, led to approximately 5-fold increase in mean exposure (AUC) and C_{max} of rosuvastatin.
This indicates that co-administration of NUBEQA may increase the plasma concentrations of other substrates of BCRP, OATP1B1 and OATP1B3 (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the respective recommendation given in the Information for healthcare professionals for these substrates should be followed when co-administering with NUBEQA.
Docetaxel
Administration of darolutamide in combination with docetaxel in patients with mHSPC did not lead to any clinically relevant changes in the pharmacokinetics of docetaxel (see section “Clinical efficacy”).

Regarding docetaxel interactions, reference should be made to the information given in the Product information for docetaxel.

P-glycoprotein (P-gp) substrates

With co-administration of darolutamide and dabigatran etexilate (a sensitive P-gp substrate), there was found to be no increase in dabigatran exposure (AUC and C_{max}).

This indicates that NUBEQA can be administered together with P-gp substrates with no clinically relevant drug-drug interactions.

CYP substrates

Darolutamide is a weak CYP3A4 inducer. Administration of darolutamide (600 mg twice daily for 9 days) prior to concomitant ingestion of a single 1 mg dose of midazolam (a sensitive CYP3A4 substrate) together with a meal led to a decrease in the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively.

In vitro, the metabolism of selected CYP substrates was not inhibited by darolutamide at clinically relevant concentrations.

This indicates that NUBEQA can be administered together with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole) with no clinically relevant drug-drug interactions.

Effect of other medicinal products on NUBEQA

CYP3A4 and P-gp inducers

Darolutamide is a substrate of CYP3A4 and P-gp.

Repeated co-administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg), together with a meal, led to a decrease in mean exposure [AUC(0-72)] and C_{max} of darolutamide by 72% and 52%, respectively.

The use of strong CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John’s wort) during treatment with NUBEQA should be avoided. Selection of a concomitant medicinal product with no or weak potential to induce CYP3A4 or P-gp should be considered.

Docetaxel

Administration of darolutamide in combination with docetaxel did not lead to any clinically relevant changes in the pharmacokinetics of darolutamide in patients with mHSPC (see section “Clinical efficacy”).

CYP3A4, P-gp and BCRP inhibitors

Darolutamide is a substrate of CYP3A4, P-gp and BCRP.

Co-administration of itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days), a strong CYP3A4, P-gp and BCRP inhibitor, with a single dose of darolutamide (600 mg on day 5 together with a meal), led to an increase in mean exposure [AUC(0-72)] and C_{max} of darolutamide by 1.7-fold and 1.4-fold, respectively.

Patients should be monitored more frequently for adverse reactions; the NUBEQA dosage should be adjusted as needed.

Medicinal products that prolong the QT interval

As androgen deprivation therapy can prolong the QT interval, concomitant administration of medicinal products known to prolong the QT interval or medicinal products known to cause torsade de pointes should be carefully considered. These include medicinal products such as class IA antiarrhythmics (e.g. quinidine, disopyramide) or class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide), methadone, moxifloxacin and antipsychotics (e.g. haloperidol).

Pregnancy, lactation

Pregnancy

NUBEQA is not indicated for treatment of women. Due to its mechanism of action, NUBEQA may cause fetal harm if used during pregnancy. No clinical data are available in pregnant women. No animal reproduction and development studies have been conducted with NUBEQA.

Lactation

NUBEQA is not indicated for treatment of women. There are no data on the appearance of darolutamide or its metabolites in human milk, on the effects on breastfed infants or the effects on milk production.

Fertility

There are no human data on the effect of NUBEQA on fertility.
Animal studies have shown that darolutamide affects the reproductive system in male rats and dogs (see section “Preclinical data”).

Effects on ability to drive and use machines

No studies on the effect of darolutamide on the ability to drive and use machines have been performed. Fatigue (very common) has been observed during treatment with darolutamide. Patients with such symptoms should be advised of the risk regarding the ability to drive or use machines.

Undesirable effects

The overall safety profile of NUBEQA is based on data from 1508 patients with nmCRPC from the ARAMIS study, 954 of whom had received at least one dose of NUBEQA, as well as data from 1302 patients with mHSPC from the ARASENS study, 652 of whom had received at least one dose of NUBEQA.

The most commonly observed adverse reaction in patients with nmCRPC who had received NUBEQA was fatigue (16% of all patients). The most common abnormalities observed in laboratory tests were neutrophil count decreased (20%), aspartate aminotransferase (AST) increased (23%) and bilirubin increased (16%). The most serious adverse reactions (Grade ≥3) in patients with nmCRPC who received NUBEQA were ischaemic heart disease (2.0%), heart failure (0.9%), fractures (0.9%) and neutrophil count decreased (0.7%).
The most commonly observed adverse reactions in patients with mHSPC who had received NUBEQA in combination with docetaxel were rash (17% of all patients) and hypertension (14% of all patients). The most common abnormalities observed in laboratory tests were an elevated level of AST (44%), as well as elevated levels of alanine aminotransferase (ALT) (42%) and bilirubin (20%). The most serious adverse reactions (Grade ≥3) in patients with mHSPC who received NUBEQA in combination with docetaxel were hypertension (6.7%) including hypertensive emergency (0.2%), ALT increased (2.8%) and AST increased (2.6%).
Regarding adverse reactions to medicinal products used in combination with NUBEQA, please refer to the information provided in the relevant Information for healthcare professionals.

Adverse reactions in patients with nmCRPC receiving NUBEQA, as well as in patients with mHSPC receiving NUBEQA in combination with docetaxel, are summarised below by system organ class and frequency. The frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10).

	NUBEQA	*NUBEQA in combination with docetaxel*
Blood and lymphatic system disorders		
Very common	Neutrophil count decreased (20%)[1]	
Cardiac disorders		
Common	Ischaemic heart disease[2] Cardiac failure[3]	
Vascular disorders		
Very common		Hypertension (14%)[4] including hypertensive emergency (0.2%)
Hepatobiliary disorders		
Very common	AST increased (23%)[1] Bilirubin increased (16%)[1]	AST increased (44%)[1] ALT increased (42%)[1] Bilirubin increased (20%)[1]
Skin and subcutaneous tissue disorders		

Very common		Rash (17%)[5, 6]
Common	Rash[7]	
Musculoskeletal and connective tissue disorders		
Common	Pain in extremities Musculoskeletal pain Fractures	
General disorders and conditions		
Very common	Fatigue (16%)[8]	

[1] based on laboratory test abnormalities.
[2] Includes arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia.
[3] Includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock.
[4] Includes hypertension, blood pressure increased, hypertensive emergency.
[5] Incidence was highest during the first 6 months of treatment
[6] Includes skin rash, drug rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, erythema, dermatitis.
[7] Includes skin rash, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, dermatitis.
[8] Including fatigue, as well as asthenia, lethargy and malaise.

Description of specific adverse reactions

Fractures

In patients with nmCRPC (ARAMIS), fractures occurred in 4.2% of patients treated with NUBEQA and in 3.6% of patients treated with placebo.

Ischaemic heart disease and cardiac failure

In patients with nmCRPC (ARAMIS), ischaemic heart disease occurred in 3.2% of patients treated with NUBEQA and in 2.5% of patients treated with placebo. Grade 5 events occurred in 0.3% of patients treated with NUBEQA and in 0.2% of patients treated with placebo. Cardiac failure occurred in 1.9% of patients treated with NUBEQA and in 0.9% of patients treated with placebo.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose-limiting toxicities were observed with this dose.
Considering the saturable absorption (see section “Pharmacokinetics”) and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity.
In the event of intake of a higher than recommended dose, NUBEQA treatment can be continued with the next dose as scheduled.
There is no specific antidote for NUBEQA and symptoms of overdose are not established.

Properties/Effects

ATC code

L02BB06.

Mechanism of action

Darolutamide is a non-steroidal androgen receptor antagonist with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain to retain strong antagonistic activity against the androgen receptor (AR).
Darolutamide competitively inhibits androgen binding, androgen receptor nuclear translocation and AR mediated transcription.
Darolutamide has strong *in vivo* anti-tumour efficacy (decreased tumour cell proliferation) leading to decreased tumour volume in xenograft models of prostate cancer including the castration-resistant prostate cancer model with VCaP cells (overexpression of AR).

Pharmacodynamics

A QT/QTc analysis (ECG-PK substudy based on triplicate ECG measurements with matched PK samples) as part of the pivotal phase 3 study (ARAMIS), as well as a concentration-QTc analysis, were performed. In the ECG-PK substudy of 520 patients, no prolongation of the mean QTcF interval (i.e. more than 10 ms) was observed after oral administration of 600 mg darolutamide twice daily compared to placebo. The concentration-QTc study confirmed these results by finding no clinically significant influence on cardiac repolarisation (QTc) for darolutamide.

Clinical efficacy

Efficacy and safety have been demonstrated in two randomised, placebo-controlled, multicentre phase III studies in patients with nmCRPC (ARAMIS) and mHSPC (ARASENS). All patients received a concomitant luteinising hormone-releasing hormone (LHRH) analogue or had undergone bilateral orchiectomy.

Non-metastatic castration-resistant prostate cancer (nmCRPC)

The efficacy and safety of NUBEQA was assessed in a randomised, double-blind, placebo-controlled multicentre phase III study (ARAMIS) in patients with non-metastatic castration resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤ 10 months. In total, 1509 patients were randomised 2:1 to receive either 600 mg darolutamide orally twice daily (n=955) or placebo (n=554).

Only patients with pelvic lymph nodes < 2 cm (transverse diameter) below the aortic bifurcation were accepted for the study. The presence or lack of metastases based on radiological examinations was reviewed by an independent central body, with metastases being identified retrospectively in 89 patients at the point t=0. Randomisation was stratified by PSADT (≤ 6 months or > 6 months) and prior use of osteoclast-targeted therapy at study entry (yes or no).

The demographic data and disease characteristics were balanced in both treatment arms. The median age was 74 years (range 48-95) and 9% of patients were 85 years of age or older. Ethnic composition was 79% white, 13% Asian, and 3% black. Most patients (73%) had a Gleason score of 7 or higher at the time of diagnosis. The median PSADT was 4.5 months. 9% of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. 76% of patients had received more than one prior anti-hormonal treatment. Patients with a history of seizures were not excluded. In the darolutamide arm, 12 patients with a history of seizures were included. Most patients (69%) had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 at study entry.

Treatment with NUBEQA was continued until disease progression (diagnosed by conventional imaging (CT, MRI, Tc99m bone scan)), unacceptable toxicity or treatment withdrawal.

The primary endpoint of the study was metastasis-free survival (MFS). The four secondary endpoints included overall survival (OS) and time to pain progression.

Treatment with NUBEQA led to a statistically significant prolongation of MFS compared to placebo (see Table 1). The MFS results were uniform across all patient subgroups, irrespective of PSADT at study entry, prior osteoclast-targeted therapy or locoregional symptoms.

At the time of the final analysis with a median follow-up of 29 months, 15.5% of patients had died in the NUBEQA arm (148/955) and 19.1% (106/554) in the placebo arm; HR 0.685 (95% CI 0.533; 0.881). Median overall survival was not reached in either treatment group. The median time to pain progression was prolonged compared to placebo (see Table 1).

Table 1: Efficacy results from the ARAMIS study

Efficacy parameter	Number of events (%)		Median (95% CI)		Hazard ratio [a] (95% confidence interval [CI]) p-value (two-sided)
	NUBEQA (n=955)	Placebo (n=554)	NUBEQA (n=955)	Placebo (n=554)	
Metastasis-free survival (MFS)	221 (23.1%)	216 (39.0%)	40.4 months (34.3, NR)	18.4 months (15.5, 22.3)	0.413 (0.341, 0.500) <0.000001
Overall survival (OS)	148 (15.5%)	106 (19.1%)	NR (56.1, NR)	NR (46.9, NR)	0.685 (0.533, 0.881)
Time to pain progression [b]	251 (26.3%)	178 (32.1%)	40.3 months (33.2, 41.2)	25.4 months (19.1, 29.6)	0.647 (0.533, 0.785)

a Hazard ratio <1 in favour of NUBEQA

b Patient reported outcomes (evaluated by Brief Pain Inventory-Short Form)

NR not reached

Metastatic hormone-sensitive prostate cancer (mHSPC)

The efficacy and safety of NUBEQA in combination with docetaxel was evaluated in a phase III, multicentre, double-blind, placebo-controlled study (ARASENS) in patients with mHSPC. Patients were required to be eligible for ADT and docetaxel therapy, as per investigator's judgment. A total of 1306 patients were randomised (1:1) and assigned to treatment with oral darolutamide 600 mg twice daily (n=651) or matched placebo (n=655), each in combination with 6 cycles of docetaxel 75 mg/m^2 each. Patients were excluded from the study if they had received prior treatment with either second-generation androgen inhibitors, CYP-17 enzyme inhibitors or chemotherapy for prostate cancer. Treatment with NUBEQA or placebo was continued until symptomatic disease progression, change in antineoplastic therapy, unacceptable toxicity, death or discontinuation of treatment.

The presence of metastasis was assessed by independent central radiological review. Patients with regional lymph node involvement only (M0) were excluded from the study. Randomisation was stratified by extent of disease (non–regional lymph node metastases only (M1a), bone metastases with or without lymph node metastases (M1b) or visceral metastases with or without lymph node metastases or with or without bone metastases (M1c)) and by alkaline phosphatase level (< or ≥ upper limit of normal, ULN)) at study entry.

The following demographic data and disease characteristics were balanced between both treatment arms. The median age was 67 years (range 41–89) and 0.5% of patients were 85 years of age or older. 52% were white, 36% Asian and 4% black. The majority of patients (78%) had a Gleason score of 8 or higher at time of diagnosis. Seventy-one percent (71%) of patients had an ECOG PS score of

0 and 29% of patients had an ECOG PS score of 1. Of the patients, 86.1% had a *de novo* tumour and 12.9% had recurrence. At inclusion in the study, 3% of patients had stage M1a, 79.5% stage M1b and 17.5% stage M1c; alkaline phosphatase was <ULN in 44.5% of patients and ≥ULN in 55.5%; the median PSA value at baseline assay was 30.3 µg/L in the NUBEQA group and 24.2 µg/L in the placebo group. Patients with a history of seizures were eligible to participate in the study and 4 patients (0.6%) were included in the NUBEQA+docetaxel treatment arm.

The primary efficacy endpoint was overall survival (OS). Another endpoint was the time to pain progression.

Pain progression was assessed using a patient questionnaire (PRO instrument), the Brief Pain Inventory-Short Form (BPI-SF), and was defined as a worsening from nadir by at least 2 points and initiation of use of a short-acting or long-acting opioid for pain over ≥7 consecutive days.

In the NUBEQA+docetaxel treatment arm, a statistically significant improvement in OS was achieved compared to the placebo+docetaxel arm, with a 32.5% (HR=0.675, p<0.0001) reduction in the risk of mortality (see Table 2 for efficacy data).

Table 2: Efficacy results from the ARASENS study

Efficacy parameter	**Number of patients with events (%)**		**Median (95% CI)**		**Hazard Ratio [b] (95% confidence interval [CI]) p-value (one-sided) [c]**
	NUBEQA+ Docetaxel (n=651)	**Placebo + docetaxel (n=654) [a]**	**NUBEQA+ Docetaxel (n=651)**	**Placebo + docetaxel (n=654) [a]**	
Overall survival (OS)	229 (35.2%)	304 (46.5%)	NR (NR, NR)	48.9 months (44.4, NR)	0.675 (0.568, 0.801) <0.0001
Time to pain progression [d]	222 (34.1%)	248 (37.9%)	NR (30.5, NR)	27.5 months (22.0, 36.1)	0.792 (0.660, 0.950) 0.0058

a 1 patient in the placebo arm was excluded from all analyses
b Hazard ratio < 1 in favour of NUBEQA
c Based on a stratified log-rank test
d Assessed by BPI-SF and initiation of use of short-acting or long-acting opioids for pain over ≥ 7 consecutive days
CRPC:castration-resistant prostate cancer
NR not reached

Pharmacokinetics

Absorption

Following oral administration of 600 mg (2 tablets of 300 mg), peak plasma concentrations of darolutamide of 4.79 mg/L (coefficient of variation: 30.9%) were reached. If the same dose is taken together with a meal, steady state is reached after 2-5 days.
The absolute bioavailability compared to an intravenous injection is approximately 30% following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions. Bioavailability of darolutamide was enhanced by 2.0- to 2.5-fold when taken with a meal. A similar increase in exposure was observed for the major metabolite keto-darolutamide.

Distribution

The apparent volume of distribution of darolutamide after intravenous administration is 119 L, indicating that darolutamide is widely distributed throughout the body to both intracellular and extracellular fluid spaces.
Darolutamide is moderately (92%) bound to human plasma proteins. The major metabolite of darolutamide, keto-darolutamide, is highly (99.8%) bound to plasma proteins.

Metabolism

Following administration of a single dose of 300 mg ^{14}C-darolutamide as an oral solution, keto-darolutamide is the only relevant major metabolite. Overall exposure in the plasma is approximately twice as high in comparison with darolutamide. Darolutamide and keto-darolutamide together account for 87.4% of the^{14} C-radioactivity in plasma, indicating that all other metabolites are of minor importance.
Darolutamide is metabolised primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1.

Elimination

The effective half-life of darolutamide and keto-darolutamide in the plasma of patients is approximately 20 hours.
The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%). A total of 63.4% of the active substance is excreted in the urine (approximately 7% unchanged) and 32.4% in the faeces. More than 95% of the dose was recovered within 7 days after administration.

Linearity/non-linearity

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure to darolutamide and the major metabolite keto-darolutamide increases linearly in a nearly dose-related

manner. Based on a saturated absorption, no further increase in exposure to darolutamide was observed at 900 mg twice daily.

Kinetics in specific patient groups

Hepatic impairment

In a clinical pharmacokinetic study, C_{max} and AUC for darolutamide were increased 1.5-and 1.9-fold, respectively, in non-cancer patients with moderate hepatic impairment compared to healthy subjects. No data are available for patients with severe hepatic impairment

Renal impairment

In a clinical pharmacokinetic study, AUC and C_{max} for darolutamide were increased 2.5- and 1.6-fold, respectively, in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) compared to healthy subjects.
A population pharmacokinetic analysis showed a 1.1-, 1.3- and approximately 1.5-fold higher darolutamide exposure (AUC) in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 m^2), respectively, compared to patients with normal renal function.
The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m^2).

Elderly patients

No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on age (41-95 years).

Children and adolescents

Safety and efficacy of NUBEQA have not been studied in children and adolescents below 18 years of age.

Genetic polymorphisms

No clinically relevant differences in the pharmacokinetics of darolutamide were observed in relation to ethnicity (white, Asian, black or African-American).

Preclinical data

Aside from reproductive organ changes observed in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Safety pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Systemic toxicity

In repeated dose toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks) at doses of ≥ 50 mg/kg/day, the main findings were changes in the male reproductive organs (decrease in organ weight with atrophy of the prostate and epididymides). These effects occurred after systemic exposures in the range of or below the anticipated human exposure (0.6-fold in rats and 1-fold in dogs, based on the AUC value). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy in seminal vesicles and mammary glands in rats, as well as hypospermia, seminiferous tubule dilatation and degeneration in dogs. Changes in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and reversed or partially resolved after 4 to 8-week recovery periods. No effects were observed in female reproductive organs in rats and dogs. There were no significant changes in clinical pathology or histopathology observed in any other organ system, including the liver.

Genotoxicity and carcinogenicity

Darolutamide did not induce mutations in the microbial mutagenesis (Ames) assay. *In vitro,* darolutamide at high concentrations did induce structural chromosome aberrations in cultured human lymphocytes. However, in the *in vivo* combined bone marrow micronucleus test and the Comet assay in the liver and duodenum of the rat, no genotoxicity was observed. Overall, darolutamide did not show a relevant genotoxic potential with regard to human use.
Long-term animal studies to evaluate the carcinogenic potential of NUBEQA have not been conducted.

Embryotoxicity/teratogenicity

Studies on developmental toxicity have not been performed.

Reproductive toxicity (fertility)

Studies on reproductive toxicity have not been performed. In repeated dose toxicity studies in rats and dogs, atrophy and hypospermia in the male reproductive system were observed, which is consistent with the pharmacological activity of darolutamide.

Other data

Darolutamide was not phototoxic *in vitro*.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Special precautions for storage

Do not store above 30°C.

Authorisation number

67521 (Swissmedic).

Packs

Packs containing 112 film-coated tablets. (B)

Manufacturer

Orion Corporation, Orion Pharma, 02101 Espoo, Finland.

Marketing authorisation holder

Bayer (Schweiz) AG, Zurich.

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